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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,050	08/20/2001	Clifford Charles Shone	1581.0800000	8265

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,050	SHONE ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,29-33,36,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,29-33,36,42,43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 11 November 2003 has been entered. Claims 1-24, 26-28, 34, 35 and 37-41 are canceled. Claims 25, 30, 31, 33 and 36 are amended. Claims 25, 29-33, 36, 42 and 43 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office action.

Withdrawn Objections and/or Rejections

Brief Description

The objection to the Specification for lacking a "Brief Description of the Several Views of the Drawing(s)," as set forth at page 4 of the previous Office Action (29 July 2003), is *withdrawn.* Applicants amended the Specification to insert a *Brief Description* (5 November 2003).

Figures

The objection to Figure 5 for being unclear, as set forth at page 4 of the previous Office Action (29 July 2003), is *withdrawn.* The examiner erroneously made this objection to Figure 1. Applicants amended the Specification to insert a *Brief Description* (5 November 2003), thus also correcting Figure 5.

Sequence Rules

The objection to the disclosure because Figure 1 and page 10 of the Specification lacked

identifying SEQ ID NO's, as set forth at page 4 of the previous Office Action (29 July 2003), is *withdrawn.* Applicants amended the Specification to insert SEQ ID NO's where appropriate (5 November 2003).

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The rejection of Claims 30 and 31 for reciting "fragments, variants and derivatives" of the SOD composition, as set forth at page 7-9 of the previous Office Action (29 July 2003), is *withdrawn.* Applicants amended the claims to remove references to "fragments, variants and derivatives" (5 November 2003).

Claim Rejections - 35 USC § 102

The rejection of Claims 25 and 36 under 35 U.S.C. 102(b) as being unpatentable over Figueiredo, et al (1997, Exp. Neurol., 145: 546-554) is *withdrawn.* Applicants amended the claims to specify that the linker in the superoxide dismutase/tetanus toxin composition is a disulfide bridge or target for a neuronal protease (5 November 2003), thus distinguishing the Invention from Figueiredo et al.

Likewise, the rejection of Claims 25 and 36 under 35 U.S.C. 102(b) as being unpatentable over Francis, et al (1995, J. Biol. Chem., 270(25): 15434-15442) is *withdrawn.* Applicants amended the claims to specify that the linker in the superoxide dismutase/tetanus toxin composition is a disulfide bridge or target for a neuronal protease (5 November 2003), thus distinguishing the Invention from Francis, et al.

Claim Rejections - 35 USC § 112, first paragraph, enablement.

The rejection of Claims 33 and 36 under 35 U.S.C. 112, first paragraph, is *withdrawn in part* (see below). This rejection was previously made at pages 6 and 7 of the previous Office Action (29 July 2003), over claims reciting a *therapeutic* agent to neuronal cells, or for use as a *pharmaceutical.* Applicants amended the claims to remove reference to *therapeutic* agents, and agents for use as a *pharmaceutical* (5 November 2003).

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph, enablement.

The rejection of Claims 25, 29-33, 36, 42 and 43 under 35 U.S.C. 112, first paragraph, for lack of enablement, is *maintained.* The specification is not enabling for the limitations of the claims wherein the recited composition of superoxide dismutase is delivered to neuronal cells or translocated into neuronal cells, or protects cells against oxidative damage. This rejection was previously made at pages 5- 7 of the previous Office Action (29 July 2003).

Claims 25, 29-33, 36, 42 and 43 are directed to a composition comprising superoxide dismutase (SOD) joined to a large fragment of *Clostridium* toxin by a linker comprising a disulfide bridge or a target of a neuronal protease. Furthermore, the claims recite compositions of SOD and *Clostridium* toxins that bind specifically to neuronal cells and that translocate the composition *into* neuronal cells.

The specification teaches a composition comprising superoxide dismutase (SOD) attached to a fragment of a *Clostridium* toxin, for the purpose of translocating the SOD into neuronal cells and thus protecting them from oxidative damage. However, the disclosure is not enabling for use of the composition to translocate SOD into neuronal cells and reduce oxidative damage. Experiments are described in which the SOD composition is applied to a culture of NG-108 neuroblastoma cells both with and without the superoxide generator duroquinone (Figure 5). Measurements were made that Applicants contend demonstrate protective effects on the cells against superoxide-induced oxidative stress. However, the methods were not described in sufficient detail to enable one skilled in the art to determine the protective effects of the SOD composition on oxidative stress in neuronal cells in the manner described. It is not known, for example, and not disclosed in the Specification, how absorbance of light at 570nm is related to oxidative stress. No experiments were performed demonstrating that the SOD/Clostridium composition was translocated into the cells. No evidence was presented that the cells were oxidatively stressed or damaged. Furthermore, the treatment groups seem indistinguishable from each other and there appears to be no concentration effect of superoxide dismutase on the measured variable- the SOD/Clostridium composition had approximately the same effect at zero concentration as the effect at a concentration of 100.

Applicants have argued (5 November 2003, pages 10 and 11) that Example 10 in the Specification is enabling for the instant Invention (see also Figure 5). Applicants have submitted abstracts as evidence that duroquinone induces oxidative stress in mitochondria, and that NG-108 cells have receptors for clostridial toxin (Wilde, et al, 2000, Eur. J. Neurosci., 12(11): 3863-3870; Wilde, et al, 1997, J. Neurochem., 69(2): 883-886; Yokasawa, et al, 1991, Toxicon.,

29(2): 261-264; Yokasawa, et al, 1989, Infect. Immun., 57(1): 272-277). Applicants also argued that use of potassium ions in the experimental baths provides evidence of neuronal stimulation of the NG-108 cells.

Applicant's arguments, submitted 5 November 2003, are not enabling for the following reasons:

The abstracts by Wilde, et al (2000) and Wilde, et al (1997) demonstrate that duroquinone induces oxidative cell death in neurons exposed to the oxidant in the absence of protective agents such as free-radical scavengers. Wilde, et al (2000) also showed that duroquinone induced endogenous neuroprotective mechanisms in the cells; for example, it caused production of superoxide dismutase (SOD) within experimental hippocampal cells (Wilde, 1997). While it is clear in Wilde, et al (2000) and Wilde, et al (1997) that duroquinone causes cell death in sensitive cortical neurons, if given in concentrations high enough to overwhelm endogenous protective mechanisms, neither abstract provides a description of a variable other than cell death that can be measured relative to duroquinone exposure.

Applicants submitted abstracts by Yokasawa, et al (1991) and Yokasawa, et al (1989) to demonstrate that botulinum toxin binds to NG-108 neuroblastoma cells. However, Yokasawa, et al (1991) showed that type D toxin *did not* bind NG-108 cells, only rat synaptosomes. Similarly, Yokasawa, et al (1989) showed that clostridium toxin *did not* bind human NG-108 cells. Regardless of whether clostridium toxin binds NG-108 cells, there is no evidence that clostridium is taken into the recited cells after binding. Importantly, there is no evidence that the *composition* of the instant Invention (SOD/clostridium fusion protein) is translocated into cells after binding, or that it then finds its way to the mitochondria.

Applicants have argued that, because there was an effect of administering the SOD composition in the presence of KCl, that this provides evidence that the SOD/clostridium fusion protein is translocated into cells. It appears from the instant data that KCl had no effect on absorbance measured, or a small negative effect. However, it is not clear from the Specification or from the data presented, what the relationship between KCl and NG-108 cell activity should be, or the presumed relationship among KCl, cell activity and uptake of the SOD composition.

Proper analysis of the Wands Factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary: 1) to measure oxidative damage in neuronal cells; 2) to inhibit oxidative damage in neuronal cells using the claimed SOD composition; 3) to overcome the lack of direction/guidance presented in the specification regarding above; 4) to overcome the complex nature of the invention; and, 5) to overcome the unpredictability of the art,--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in the matter specified.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
4/17/04

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